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TIIA JÄMSÉN

Endovascular and Surgical Revascularizations for Chronic Lower Limb Ischemia

5- to 10-Year Outcome

Doctoral dissertation

To be presented by permission of the Faculty of Medicine of the University of Kuopio for public examination in Kuopio University Hospital Auditorium, on Friday 20th September 2002, at 12 noon

Departments of Clinical Radiology and Surgery
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ABSTRACT

BACKGROUND: This study was performed to define the long-term outcome of axillofemoral bypass surgery and infrainguinal endovascular and surgical revascularizations in the treatment of chronic lower limb ischemia. Outcomes are reported separately for claudicants and patients with chronic critical limb ischemia (CLI).
PATIENTS AND METHODS: The study population consisted of 585 consecutive, non-randomised patients with 784 treated limbs. Cumulative primary, secondary and total patency and patient survival rates were determined according to life table analysis. Furthermore, limb salvage and life with limb –rates for limbs treated for CLI were calculated. In claudicant patients, development of CLI was determined. Factors affecting long-term outcome of these procedures were defined.
RESULTS: The primary patency rate (± standard error of estimate (SEE)) of axillo-femoral bypass surgery in 84 patients was 57 % (±0.09) at five years. Thrombectomy was required almost four times more frequently in uni- than in bifemoral grafts (p=0.03). For 85 infrainguinal bypasses among claudicants, the primary patency rate at seven years was 51 % (±0.07). Endovascular treatment of 218 limbs in claudicants resulted in 20 % (±0.03) patency at seven years, and 14 % (±0.03) at ten years. In both surgical and endovascular procedures, a higher number of diseased vessels in the treated limb was associated with decreased long-term patency. Patients who had undergone invasive treatment for claudication had similar clinical long-term benefit irrespective of the type of primary intervention. Furthermore, patients with severe claudication had definite long-term benefit from treatment. In claudicant patients, the total patency rate, including all infrainguinal invasive treatments for lower limb ischemia, was 41 % (±0.03) at ten years. In limbs with CLI, both infrainguinal endovascular (116 limbs) and surgical (168 limbs) procedures resulted in 60 % (SEE <0.10) limb salvage rate at eight years. Diabetes increased the risk of major amputation three-fold. Survival of patients with CLI was poor, with only 14-21 % of the patients alive at eight years after treatment.
CONCLUSIONS: Patients with severe claudication have definite long-term clinical benefit from infrainguinal revascularizations. In CLI, infrainguinal endovascular and surgical treatments result in similar long-term limb salvage rates. Survival in CLI patients is poor.

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Medical Subject Headings: radiology/interventional; vascular surgical procedures; extremities/blood supply; leg/blood supply; angioplasty/balloon; ischemia/surgery; chronic disease; intermittent claudication; follow-up studies; treatment outcome; vascular patency; limb salvage; survival analysis

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ABBREVIATIONS

ABI	Ankle-brachial systemic blood pressure index
ASA	Acetylsalicylic acid
CI	Confidence interval
CLI	Chronic critical limb ischemia
DSA	Digital subtraction angiography
OR	Odds ratio
PAOD	Peripheral atherosclerotic occlusive disease
PE	Primary endovascular treatment
PS	Primary surgical treatment
PTA	Percutaneous transluminal angioplasty
PTFE	Polytetrafluoroethylene
SD	Standard deviation
SEE	Standard error of estimate
SFA	Superficial femoral artery
TASC	Trans Atlantic Inter-Society Consensus
US	Ultrasound

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles, which are referred to in the text by their Roman numerals:

I Jämsén T, Tulla H, Loponen P. Axillofemoral bypass operations in Kuopio University Hospital 1985-1996. Ann Chir Gynaecol 1999; 88: 269-275.

II Jämsén T, Tulla H, Manninen H, Räisänen H, Lahtinen S, Aittola V, Jaakkola P. Results of infrainguinal bypass surgery: An analysis of 263 consecutive operations. Ann Chir Gynaecol 2001; 90: 92-99.

III Jämsén T, Manninen H, Tulla H, Matsi P. The final outcome of primary infrainguinal percutaneous transluminal angioplasty in 100 consecutive patients with chronic critical limb ischemia. J Vasc Interv Radiol 2002; 13: 455-463.

IV Jämsén T, Manninen H, Jaakkola P, Matsi P. Long-term outcome of patients with claudication after balloon angioplasty of the femoropopliteal arteries. Radiology 2002; 225: in press.

V Jämsén TS, Manninen HI, Tulla HE, Jaakkola PA, Matsi PJ. Infrainguinal revascularization for claudication: Total long-term outcome of endovascular and surgical treatment. Submitted for publication.

 Unpublished results are also presented in this document.

CONTENTS

1. INTRODUCTION

Claudication and chronic critical limb ischemia (CLI) are the main manifestations of chronic lower limb ischemia caused by peripheral atherosclerotic occlusive disease (PAOD). Claudication expresses as recurrent lower extremity pain following physical activity, for instance a particular walking distance, which disappears within minutes after cessation of that activity. CLI is considered a more severe form of limb ischemia presenting as rest pain and/or tissue defects in the affected limb. In CLI, limb viability is threatened. PAOD is a risk marker for other atherosclerotic diseases, such as coronary artery and cerebrovascular diseases. Survival in patients with chronic limb ischemia is low, mostly because of complications related to systemic atherosclerosis.

In many cases, chronic lower limb ischemia can be managed by active, non-invasive treatment. If it proves insufficient or if ischemia is severe from clinical onset, invasive methods including endovascular and surgical procedures can be considered. Endovascular and surgical treatments are not competing modes of therapy, but in most clinical situations mainly complementary procedures due to differences in applicability, safety and outcome among different subgroups of patients.

There is no comprehensive consensus on the preferred type of procedure in particular lesions and clinical disease entities. The current Trans Atlantic Inter-Society Consensus document (TASC) (1) gives some guidelines, but they are confined to a proportion of lesions encountered in clinical practise. The picture we have of long-term outcome of invasive treatments in lower limb ischemia is incomplete, especially regarding endovascular treatment. More details of long-term outcome of these methods would facilitate clinical decision-making. Another problem is lack of studies reporting long-term outcomes for patients with claudication and CLI separately. As patient characteristics, distribution and extent of lesions, treatment objectives and outcome are different in these two groups, studies with mixed results of claudicants and CLI patients make interpretation of the results difficult and decreases their clinical usefulness. Inconsistent practise on reporting the outcome of revascularization procedures has further complicated matters, but publication of recommended reporting standards has improved this situation (2).

Patients with aortoiliac atherosclerosis and high operative risk can be treated with axillofemoral bypass surgery. The majority of studies on axillofemoral bypasses have been made before the large-scale introduction of externally supported grafts in clinical practise in the 1980s, which was expected to improve the long-term outcome of these extra-anatomic bypasses.

This series of studies aimed to define the long-term outcome of axillofemoral bypass surgery and infrainguinal endovascular and surgical revascularizations in the treatment of chronic limb ischemia, as well as associated outcome determinants. A large population of unselected, consecutive patients with lower limb ischemia was chosen as study patients. Outcomes are reported separately in claudicants and patients with CLI according to current reporting standards.

2. REVIEW OF THE LITERATURE

2.1. Chronic limb ischemia

Chronic lower limb ischemia results from an imbalance between the supply and demand of oxygenated blood in the lower extremities. Deterioration of arterial circulation is in most cases due to atherosclerotic lesions which cause narrowing or obstruction in the vessels (1). Other causes of chronic lower limb ischemia, such as embolization, aneurysms, popliteal entrapment syndrome, collagen diseases, vasculitides and Buerger's disease (3, 4) are beyond the scope of this study.

2.1.1. Claudication

Claudication refers to lower extremity pain, discomfort or weakness that is consistently produced by the same amount of walking or equivalent muscular activity in a given patient and that is promptly relieved by cessation of that activity (2). It is caused by any occlusive lesion in the arterial supply of the limb muscles that interferes sufficiently enough with blood flow to produce ischemic pain with exercise (5), when oxygen consumption in the muscles is increased. Claudication is caused by aortoiliac occlusive disease in the majority of patients younger than 40 years of age, whereas femoropopliteal disease is usually responsible for the symptoms in older patients (6, 7). In general, the lesions are focal stenoses. Several factors, e.g. history of smoking, diabetes, hypertension, hyperlipidemia, male sex, advanced age and hypercoagulable states, have been associated with increased risk of claudication (5, 8). The prevalence of claudication increases with age (9). According to a Dutch population-based study, the prevalence of claudication is 1.6 % in a population over the age of 55 years, varying from 0.7 % in women aged 55-59 years to 6.0 % in men aged 85 years or older (10). In

Finland, the prevalence of claudication has been reported to be 4.6 % in men and 2.8 % in women in the age group between 50 and 59 years (9).

Claudication reduces the quality of life (11), due to pain, discomfort, and decreased physical and social functioning (12, 13). Nine to fifteen percent of all claudicants have been reported to require revascularizations during a mean follow-up of four to seven years (14-16). The development of CLI in a claudicant population without revascularizations has been 2.5 % per year in the long-term (15). In a clinical study with 195 patients, 24 % of limbs with claudication had progressed to CLI without invasive interventions at 5 years and 41 % at 8 years according to life table analysis (17). The cumulative development of CLI was 30 % within 10 years among 1244 male claudicants referred to a vascular laboratory (18). In that study, diabetes and lower ankle-brachial pressure index (ABI) predicted the development of CLI. In a review article, the estimated risk of developing CLI was found to be 4 times higher in diabetics than in non-diabetics, whereas the risk was 3 times higher in smokers than in non-smokers (19). ABI less than 0.5 has also been associated with increased risk of CLI development (15). In a randomised study with unselected, stable claudicants, 2.2 % of the control group underwent amputation during 12 months, compared with 1.1 % in the invasive treatment group (20). In another study, the cumulative rate of major amputations among conservatively treated claudicants was 1.4 % per year during long-term follow-up (15). However, in that study revascularizations were performed if CLI developed.

Mortality is higher among claudicant patients than among the general population. It has been 2- to 2.5-times that of the general population, with 30-42 % mortality rates at five years and 50-65 % at ten years (15, 16, 21). Most of this increase is caused by coronary artery and cerebrovascular diseases due to systemic atherosclerosis (1). Advanced age, coronary artery disease, cerebrovascular disease, male sex, low ankle pressures or ABIs, smoking, diabetes and hypertension have been found to associate with decreased survival among claudicants (1, 15, 16).

2.1.2. Chronic critical limb ischemia

CLI is the most severe clinical manifestation of PAOD. However, in a recent study 37 % (37/100) of patients with CLI never experienced the earlier clinical stage of PAOD in the form of claudication before critical ischemia developed, many because they were too sedentary to claudicate (22). The European consensus document defined CLI by the presence of persistently recurring ischemic rest pain requiring analgesics for more than 2 weeks or by non-healing ischemic ulcer or gangrene of the foot or toes with an ankle systolic pressure less than 50 mmHg (23). In the North American definition, the pressure limits for CLI are 40 mmHg for rest pain and 60 mmHg for tissue loss (2). CLI occurs when arterial stenoses or occlusions impair blood flow to such an extent that despite compensatory mechanisms such as collateral formation, the nutritive requirements of peripheral microcirculation cannot be met (4). It is often caused by multilevel disease with main lesions in infrainguinal vessels (24).

The estimated incidence of CLI in European populations is 400-650 per million per year, peaking in the age group of 70-79 years for both genders (25-27). The risk factors of CLI are the same as those of claudication, but patients presenting with CLI are older, with higher incidences of diabetes, renal insufficiency and coronary artery disease (28).

Diabetes in particular often produces profound limb ischemia by affecting both systemic arteries and tissue capillaries: about 30 % of patients developing CLI are diabetics (27).

CLI threatens the patient's life and limb (29). In a study of 105 patients with unrevascularized CLI, only 28 % were alive without major amputation in the affected limb at one year according to life table analysis (30). The primary aim, at least for all independent, mobile patients with CLI, is revascularization, to provide sufficient blood flow to relieve rest pain and heal skin lesions in order to save the limb (4). It is impossible to describe the natural history of patients with CLI, because almost all limbs are considered for revascularization. The minority of patients with unrevascularized CLI are in no way representative of the whole group (30). In those patients, life expectancy is minimal, operative risks are high, and independent living is impossible due to other medical conditions, or there are no prospects of saving a viable limb.

According to a register-based study, revascularizations for CLI were performed in 203 patients per million inhabitants per year in Finland during 1993-1994 (29). Almost half (44 %) of these operations were endovascular. The introduction of modern revascularization techniques was associated with a 60 % reduction in the total amputation rate (31). According to another report, the percentage of major amputations among patients with CLI decreased from 49 % to 14 % between 1974 and 1989, possibly for the same reason (24). In recent reports, only 5-15 % of limbs with CLI have been primarily amputated without an attempt at revascularization (24, 32, 33). However, in 1993-1994 216 major amputations per million inhabitants per year were performed in Finland for limb ischemia, despite revascularizations (29). Limb loss markedly decreases the quality of life and increases expenses due to rehabilitation and nursing

(34, 35). Amputation has been associated with higher operative mortality and longer hospital stay than revascularization (27). A significantly greater proportion of patients require long-term institutional support after amputation than after revascularization (27). Factors associated with increased risk of major amputation include CLI with tissue loss, bilateral CLI and renal failure requiring dialyses (30, 36-38).

In a Swedish register-based study, cumulative mortality in patients with CLI was 23 % at one year (38). In clinical trials, ten-year mortality rates of 70 % and 87 % were obtained among CLI patients (39, 40). In a clinical study with CLI patients, the cause of death was coronary artery disease in 47 % (23/49) and cerebrovascular disease in 10 % (5/49) (41). Factors associated with increased mortality in patients with CLI include a history of previous myocardial infarct or stroke, diabetes (36), bilateral CLI (30), renal failure requiring dialyses (37), and major amputation (38, 42).

2.1.3. Diagnosis of chronic limb ischemia

A thorough anamnesis combined with clinical examination are the cornerstones when evaluating a patient with suspected limb ischemia. Other manifestations of atherosclerosis, such as coronary artery and cerebrovascular diseases, should also be looked for, because they significantly affect the prognosis of patients with PAOD (36). Detecting risk factors for PAOD, for instance high blood glucose levels, hypertension or hyperlipidemia (8, 43), is important in order to treat them. According to a recent population-based study, smoking is the strongest independent determinant of PAOD development in elderly people (43).

According to TASC document, ankle pressures and ABIs at rest should be measured in all patients, including the asymptomatic limb. Normal ABI is above 1.00, and values less than 0.9 at rest are indicative of PAOD (5). False high values can be measured especially in diabetic patients who often have incompressible crural arteries due to medial sclerosis (44).

A treadmill exercise test is performed to objectively measure walking performance in patients with claudication. The patient walks at a standard speed and grade on a treadmill until claudication pain is experienced or a time limit has been reached. If a significant arterial occlusive lesion exists, there will be a significant decrease in the ABI from resting to postexercise level (5). Chronic lower limb ischemia is graded according to Fontaine and Rutherford classifications (2) by non-invasive testing (Table 1).

A digital subtraction angiography (DSA) including infrarenal aorta and pedal arteries should be performed to plan invasive treatment (1). Recently, magnetic resonance angiography (45) and duplex ultrasound (US) scanning (46-48) have been increasingly used as a substitute for, or to limit the extent of, conventional angiography in selected patients, especially if renal function is impaired. Furthermore, modern multi-detector row CT angiography shows promise in peripheral vascular imaging (49).

Table 1. Clinical categories of chronic limb ischemia according to Rutherford and Fontaine.

Grade	Category	Clinical description	Objective criteria
Rutherford			
0	0	Asymptomatic, no hemodynamically significant occlusive disease	Normal treadmill test
	1	Mild claudication	Treadmill exercise completed, postexercise AP greater than 50 mmHg but at least 20 mmHg below normal
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Treadmill exercise cannot be completed and postexercise AP less than 50 mmHg
II	4	Ischemic rest pain	Resting AP less than 40 mmHg, flat or barely pulsatile ankle or metatarsal pulse volume recording, TP less than 30 mmHg
III	5	Minor tissue loss: non-healing ulcer or focal gangrene	Resting AP less than 60 mmHg, ankle or metatarsal pulse volume recording flat or barely pulsatile, TP less than 40 mmHg
	6	Major tissue loss extending above transmetatarsal level	Same as for category 5
Fontaine			
I		Asymptomatic, no hemodynamically significant occlusive disease	
IIA		Mild claudication, walking distance more than 200 meters	
IIB		Moderate to severe claudication, walking distance less than 200 meters	
IIIA		Ischemic rest pain, AP greater than 50 mmHg	
IIIB		Ischemic rest pain, AP less than 50 mmHg	
IV		Nonhealing ischemic ulcer or gangrene	

Note.— AP= ankle pressure.
TP= toe pressure.

2.2. Conservative treatment of chronic limb ischemia

In claudicants, the TASC document recommends conservative treatment including exercise training for at least three months, before invasive treatment is considered (5). In patients with CLI, it is important to start the treatment promptly, and when invasive treatment is feasible it should be combined with conservative methods (4).

Treatment of systemic risk factors is essential in order to the prevent progression of symptoms in the affected limb and to restrict the underlying systemic atherosclerotic process. The progression of PAOD from asymptomatic to claudication to rest pain is associated with smoking (4), and the outcome of invasive treatment also seems to be negatively affected by smoking (50, 51). Therefore, all patients with PAOD should be advised to stop smoking. Diabetes adversely affected the long-term outcome of limb ischemia, even in revascularized limbs (52), and therefore measures should be taken to normalise blood glucose levels (5). Hyperlipidemia, hypertension and hypercoagulable states should also be treated aggressively. Furthermore, in patients with CLI, pain and any infection in the ischemic limb should be controlled (4).

To reduce the risk of cardiovascular morbidity and mortality, all patients with PAOD are recommended to have long-term medication of low-dose aspirin or other approved antiplatelet drug, unless contraindicated. However, such drugs have no proven effect on limb ischemia itself (1). No pharmacological agent has proved efficacious enough in either providing significant reduction or elimination of symptoms of claudication to gain widespread acceptance for improving walking (5). Oral anticoagulants are recommended in claudicants only in hypercoagulable states (5). There is a need to determine whether long-term oral antithrombotic therapy is useful in limb salvage. In patients with CLI, prostacyclin analogue iloprost can be used if revascularization is not possible and early amputation is still avoidable (4). Furthermore, PGE_1 alprostadil has been associated with better CLI recovery, though it did not affect mortality or amputation rates (36).

Exercise training programmes have been shown to improve walking distance in claudicants by up to 210 % (53). However, in a randomised study with unselected claudicants, it offered no therapeutic advantage compared with untreated controls at one year, whereas invasive treatment improved maximum walking distance and ABI statistically significantly compared with exercise training (20). Furthermore, the efficacy of exercise training in the long-term is unknown (53). In two prospective randomised trials, exercise produced shorter maximum walking distances and smaller increases in ABI than percutaneous transluminal angioplasty (PTA) at two (54) and at six years (55), but the differences were not statistically significant. However, in the former study, patients had mild to moderate claudication with mean maximum walking distance 206 m and ABI 0.73 at baseline. In the latter study the severity of claudication was not clearly defined. In addition, compliance in exercise training is low (49-63 %), often due to osteoarthritis, coronary artery disease and non-medical causes (7, 20). However, excercise training is inexpensive, there is no exposure to operative complications, and it causes favourable changes in lipid profiles (7). Recently, the question whether exercise could also produce harmful effects in claudicants has been raised. Exercise in patients with claudication have been shown to increase oxidant stress (56), and tubular and glomerular dysfunction were detected in claudicants after exercise (57).

2.3. Invasive treatment of chronic limb ischemia

According to the recent consensus document, invasive treatment of claudication is indicated only in selected patients with life-style limiting disease in whom exercise training combined with other conservative methods has failed (5). Endovascular and surgical treatments of lower limb ischemia are not competing modes of therapy, but more like complementary procedures (58). Surgery is relatively seldom required in patients with claudication. It may be considered, if invasive treatments are required and PTA is not possible or fails (5). In CLI, if there is a balanced choice between an endovascular and surgical procedure for a particular patient, then the former is preferred because it avoids anesthesia, poses a lesser systemic stress and has fewer serious complications (4). According to a Finnish register-based study, 31 % of all endovascular revascularizations for chronic limb ischemia have been performed for CLI (28).

According to current recommendations in both claudication and CLI, surgery is the procedure of choice in complete common femoral artery or superficial femoral artery (SFA) occlusions or in complete popliteal and proximal trifurcation occlusions (1). The TASC document recommends PTA as the first choice of invasive treatment in patients with a single femoropopliteal stenosis up to 3 cm in length (1). More evidence is required to make any firm recommendations about the best treatment for all other types of infrainguinal lesions (1). Although PTA has an established role in the treatment of focal femoropopliteal disease (59, 60), the precise definition of "focal" is open to debate and the threshold of what can and should be treated with endovascular procedures is shifting towards more severe and longer lesions (52, 61). Combining endovascular and surgical methods either simultaneously or sequentially over time can be practical when there are several lesions of varying length and severity in separate segments, or in cases with graft stenosis or failed PTAs (24, 62, 63). A simultaneous combined approach is facilitated by the introduction of operating rooms equipped with high quality angiographic equipment and angiographic suites with improved sterility conditions.

2.3.1. Endovascular treatment

Femoropopliteal PTA

PTA became widely used after the introduction of balloon catheters by Grüntzig in 1974, although imaging-guided catheter intervention for PAOD had already been described in 1964 (64). Primary technical failures are encountered in 4-11 % of the PTAs, especially in occlusions (65-67). Reobstruction of the dilated segment after successful PTA is another problem, impairing long-term patency. Processes that can cause reobstruction include vascular remodelling and myointimal hyperplasia (68). However, when reobstruction developed, late success of a repeated PTA was similar to that of a primary one (66), and previous PTA does not preclude performance of bypass grafting, if required (69). In a meta-analysis, PTA was found more cost-effective than surgery in selected patients with focal femoropopliteal disease (59), partly because the complication rate was lower (59) and hospital stays shorter (70) with similar outcomes (71).

Primary patency rates in femoropopliteal PTA range between 26 % and 58 % at five years (Table 2). Operative indication (claudication vs. CLI) (50, 72) and the type of lesion (stenosis vs. occlusion) (66, 72) have been associated with long-term outcome, but in other studies the type of lesion has not been a determinant of long-term outcome (52, 73). In limbs with poor runoff, results have been inferior to those in limbs with good runoff (50, 52, 66, 67). In critically ischemic limbs, dilation of short stenoses, even in the presence of multiple distal lesions, may improve distal flow sufficiently to promote wound healing (32). The length of the treated lesion(s) has been found to affect primary patency (52, 73, 74). In a recent study with CLI limbs, five-year primary patency was significantly lower in SFA occlusions longer than 5 cm than in shorter occlusions (12 % vs. 32 %, $p<0.01$) (69). Primary patency has been reported to be poorer in patients with diabetes or renal failure (52). Furthermore, in one study long-term outcome was worse in smokers than in non-smokers (50).

Table 2. Long-term outcome of femoropopliteal PTAs.

First author	Year	Study type	Claudication (%)	Limbs n=	Occlusions (%)	Cumulative primary patency (± SEE %)				Lesion length (cm)
						3 years	4 years	5 years	6 years	
Gallino (58)	1984	R S	61	280	23	-	-	58 (-)	-	n.d.
Johnston (66)	1992	P S	80	254	38	51 (4)	44 (4)	38 (4)	36 (5)	n.d.
Hunink (72)	1993	P S	58	131	10	-	-	45 (5)	-	mainly <5
Matsi (73)	1994	P S	100	140	49	42 (5)	-	-	-	5.1
Stanley (67)	1996	R S	74	200	41	38 (6)	30 (7)	26 (8)	-	n.d.
Martin (75)	1999	R S	74	88	6	57 (5)	44 (6)	37 (7)	29 (9)	mainly <3
Karch (76)	2000	R S	59	112*	7	57 (7)	52 (9)	-	-	2.3
Clark (52)	2001	P M	58	219	11	69 (5)	-	55 (7)	-	4
Löfberg (69)	2001	R S	0	121	35	27 (-)	-	27 (-)	-	n.d.

Note.— P= prospective.
R= retrospective.
S= single centre.
M= multicentre.
* = number of lesions.
n.d.= not defined.

In a population of patients 74 % of whom were claudicants, 47 % (41/88) had undergone vascular reoperation (PTA or surgical revascularization) at 15 months after the primary PTA (75). In another study with similar patients, 26 % (51/200) required further revascularizations during 2-year follow-up (67). A late revascularization rate of 33 % (25/76) at five years was found in a population where 64 % were claudicants (77). Bypass surgery was reported in 42 % (59/142) of critically ischemic limbs within a year after the primary PTA (78). Limb salvage rates following femoropopliteal PTA in limbs with CLI have been 86-91 % at five years (Table 3).

Table 3. Cumulative limb salvage rates after infrainguinal revascularizations in critically ischemic limbs.

First author	Year	Study type	No. of limbs	Cumulative limb salvage (± SEE %)				Level	Method
				1 years	3 years	5 years	10 years		
Landry (79)	2002	P S	198	98 (1)	93 (2)	89 (3)	75 (7)	FP 49 %	B
Laurila (80)	2000	R M	38	-	91 (-)	-	-	FP	B
Luther (81)	1996	R M	130	87 (-)	82 (-)	77 (-)	-	FP	B
Watelet (40)	1997	P S	93	-	-	-	74 (<10)	FP	B
Wilson (82)	1996	R S	171	91 (-)	86 (-)	-	-	FP 74 %	B
Cavillon (83)	1998	R S	162	65 (5)	-	61 (10)	-	FD	B
Luther (84)	1997	R M	187	81 (-)	76 (-)	71 (-)	-	FD	B
Sayers (85)	1993	R S	78	-	67 (<10)	-	-	FP 23 %	B
Albäck (50)	1998	R S	50	84 (-)	-	-	-	FP	E
Hunink (72)	1993	P S	55	91 (5)	91 (5)	91 (5)	-	FP	E
Laurila (80)	2000	R M	86	-	76 (-)	-	-	FP	E
Matsi (86)	1993	P S	117	56 (5)	49 (7)	-	-	FP 58 %	E
Söder (87)	2000	P S	72	80 (5)	-	-	-	FD	E

Note. — P= prospective.
R= retrospective.
S= single centre.
M= multicentre.
FP= femoropopliteal.
FD= femorodistal.
B= bypass operation.
E= endovascular treatment.

Infrapopliteal PTA

Outcome of infrapopliteal PTA is less well documented than that of femoopopliteal procedures. The role of infrapopliteal PTA in the treatment of claudication has not been established (5). According to recent recommendations, PTA is the procedure of choice in single stenoses shorter than 1 cm in infrapopliteal arteries in CLI (4). Infrapopliteal PTA was technically successful in 98 % (39/40), with a 2-year primary patency rate of 68 % in a population of patients where 50 % were claudicants (88). In another study, a primary patency rate of 48 % at 18 months was achieved in limbs with CLI following infrapopliteal PTA (87).

One study suggested that the more distal PTA, the worse limb salvage rate (78). In infrapopliteal PTA, 1-year limb salvage has ranged from 77 % (88) to 80 % (±0.05) (87), and from 72 % (±0.09) (89) to 87 % (±0.09) (90) at three years. Factors associated with poor limb salvage after infrapopliteal PTA include renal insufficiency, lack of angiographic improvement at the site of the most severe ischemia (87) and distal runoff (90).

Other endovascular methods

An intraluminal stent is a metallic, tubular net device used to restore or maintain patency of the obstructed vessel after dilation or recanalization. Stent placement is beneficial in preventing elastic recoil and in rescuing PTA failures, as it creates a homogenous lumen in cases of dissections, intimal flaps or residual stenoses (68, 91). However, routine femoropopliteal stent placement does not offer any advantage over PTA in terms of long-term patency rates (68, 91, 92). Atherectomy was developed to treat short, eccentric lesions by shaving off atheroma plaque using a special cutting catheter. In a recent randomised study, it did not provide any advantage over conventional femoropopliteal PTA during 2-year follow-up (93). Experience with endovascular stent-grafts (a stent covered with a vascular graft material) in the femoropopliteal segment has started to accumulate: the results vary widely, with one year primary patency rates of 23-79 % (94-97). Selective intra-arterial thrombolysis can be useful in conjunction with PTA, atherectomy, stent placement or surgical treatment in patients with chronic ischemia presenting with recently worsened symptoms or in those with angiographic evidence of thrombotic component in the occlusion (98).

2.3.2. Surgical treatment

Axillofemoral bypass on aortoiliac disease

Aortobifemoral bypass surgery and aortoiliac endovascular interventions are considered standard treatments in aortoiliac occlusive disease (1). However, axillofemoral bypass surgery is associated with lower operative stress compared with aortobifemoral revascularization due to the subcutaneous position of the graft and lack of aortic clamping (99). Patients with limited iliac lesions are best candidates for endovascular procedures (1).

Axillofemoral bypass was described in 1963 as an alternative to anatomic aortobifemoral reconstruction in patients with aortoiliac atherosclerosis (100, 101). A cross-limb was later added to form an axillobifemoral graft (102). The use of axillofemoral bypass is indicated when there is exceptional surgical risk, or an abdominal approach is contraindicated (99, 103). This method is considered safe with lower operative mortality and morbidity than in aortobifemoral bypass operations (4). However, there is a consensus regarding the inferior patency of axillofemoral bypasses compared with aortobifemoral reconstructions. Despite the fact that the introduction of externally supported polytetrafluoroethylene (PTFE) and dacron grafts has improved the long-term outcome of these procedures (99, 104), axillofemoral bypasses have mostly been reserved for high-risk patients with CLI, although they have also been used in selected cases in claudicants as well (105, 106).

Primary patency rates for axillofemoral bypasses have ranged between 54-85 % at three years and 29-85 % at five years (Table 4). Secondary patency rates have seldom been reported, or the definition for patency has not been given. In one study, a secondary patency rate of 75 % at five years was reported following a primary patency of 47 % at the same time point (107).

Table 4. Primary patency rates of axillofemoral bypass grafts.

First author	Year	No. of operations	Study type	Claudicants (%)	Cumulative primary patency rate (± SEE %)	
					3 years	5 years
Donaldson (103)	1986	100	R S	19	54 (<10)	29 (<10)
Schultz (104)	1986	56	R S	55	-	75 (>10)
Rutherford (108)	1987	27	R M	-	62 (14)	62 (22)
Harris (99)	1990	76	R M	-	85 (8)	85 (-)
el-Massry (109)	1993	79	R S	38	-	78 (<10)
Martin (105)	2000	60	R S	22	72 (8)	63 (11)

Note.— R= retrospective.
S= single centre.
M= multicentre.

Long-term patency has been shown to be better in claudicants than in patients with CLI (106), although the reverse has also been reported (104). On the basis of preoperative angiographic classification, iliac inflow occlusion and patency of both femoral outflow vessels seemed to favour long-term patency (106). The absence of arterial occlusive disease distal to the femoral anastomosis has been associated with better patency in some studies (106, 108), while in other studies runoff status has failed to show any effect (104, 105). The question of the superiority of axillobifemoral reconstructions over axillounifemoral is still open to debate, as no randomised studies have been done (105, 110). The reported percentage of patients requiring further revascularizations has ranged from 13 % with a 13-month follow-up (105) to 32 % after follow-up of 22 months (103). Limb salvage rates in patients with CLI have been reported to be 78-81 % at five years following axillofemoral bypass surgery (107, 111).

Infrainguinal bypass

Infrainguinal bypass operations have been performed since 1949 (112). Bypasses are constructed of either autologous veins, synthetic prostheses, umbilical vein, or combinations of those. In infrainguinal bypasses, graft stenosis is a significant problem: it has been detected in 22-30 % of both venous and prosthetic grafts (82, 113-115). Localised perioperative vascular injury has been associated with late development of infrainguinal vein graft stenoses (116). Attempts have been made to improve long-term outcome by developing surveillance programmes to detect failing grafts before occlusion. In single centre studies, early recognition and revision of stenotic graft lesions has been found to improve cumulative patency (115) and produce excellent limb salvage rates (117). In a randomised study, intensive duplex US surveillance identified failing vein grafts and lead to higher long-term patency rates compared with those after routine follow-up examination (118). However, in another randomised study no difference was found in patency or limb salvage rates between these two surveillance methods (119). Recently, duplex scan surveillance was found to be effective in CLI patients leading to a reduction of amputations and costs (120). During recent years, up to 70 % of graft interventions have been endovascular (114), which is the currently advocated method in the treatment of focal graft stenoses less than 2 cm in length (121, 122).

Long-term primary and secondary patency rates after infrainguinal bypasses vary according to operative indication, graft material and the level of distal outflow (Table 5). According to two randomised studies, autologous vein produces better patency rates than PTFE in above-knee femoropopliteal bypasses (123, 124). Also in more distal bypasses, patency rates of vein grafts seem superior to PTFE grafts (51, 59). Whether the vein should be mobilised or left in situ is a matter of debate. In a prospective, non-randomised study with 387 grafts, no difference was found in primary patency between in situ and non-reversed vein grafts (125). However, in other studies, reversed great saphenous femoropopliteal vein grafts achieved better long-term primary patency than in situ grafts (40, 126). In synthetic grafts, below-knee distal anastomosis has been reported to be the principal predictor of graft failure (127). Distal vein cuff has been shown to improve outcome in below-knee femoropopliteal PTFE bypass grafts, whereas no benefit was found in above-knee grafts (128). Arteriovenous fistula, in order to improve graft flow, seems not to confer any additional advantage over vein cuff in femoro-infrapopliteal PTFE bypasses (129). Smoking appears to increase the risk of infrainguinal bypass occlusion (51), and poor preoperative runoff has been found to predict graft failure in infrainguinal bypasses (130, 131). Gender was not found to affect outcome after femoropopliteal bypass (132).

Table 5. Long-term outcome of infrainguinal bypass surgery.

First author	Year	Study type	Outflow	Claudi-cation (%)	Limbs n=	Vein graft (%)	Cumulative primary patency (± SEE %)				Cumulative secondary patency (± SEE %)		
							3 yrs	4 yrs	5 yrs	10 yrs	3 yrs	5 yrs	10 yrs
Wolf (71)	1993	P M	FP	69	51	n.d.	-	57 (-)	-	-	-	-	-
Luther (81)	1996	R M	FP	0	130	100	63 (-)	-	61 (-)	-	75 (-)	72 (-)	-
Wilson (82)	1996	R S	FP 74%	35	275	91	49 (-)	-	-	-	69 (-)	-	-
Watelet (40)	1997	P S	FP	2	100	100 RE	-	-	-	65 (<10)	-	-	70 (<10)
”	”	P S	”	”	”	100 IS	-	-	-	42 (<10)	-	-	65 (<10)
Byrne (133)	1999	R S	FP AK	100	165	10	70 (6)	-	48 (8)	-	72 (6)	50 (8)	-
”	”	R S	FP BK	100	150	97	77 (6)	-	70 (8)	-	81 (5)	78 (7)	-
Sayers (85)	1993	R S	FP 23%	0	78	100	29 (<10)	-	-	-	64 (<10)	-	-
Luther (84)	1997	R M	FD	0	187	100	53 (-)	-	47 (-)	-	66 (-)	53 (-)	-
Cavillon (83)	1998	R S	FD	0	162	81	-	-	35 (8)	-	-	46 (9)	-
Byrne (133)	1999	R S	FD	100	94	100	86 (6)	-	79 (10)	-	90 (5)	83 (9)	-

Note.— P= prospective.
R= retrospective.
S= single centre.
M= multicentre.
FP= femoropopliteal bypass.
FD= femorodistal bypass.
AK= above-knee.
BK= below-knee.
RE= reversed vein graft.
IS= in situ vein graft.

The rate of reoperations following infrainguinal bypass surgery has varied between 15 % and 28 % with a follow-up from 2 to 4 years (123, 133, 134). Altogether 47 % of limbs required another revascularization by 5 years after infrainguinal bypass surgery in a population of patients including 40 % claudicants (77).

A correlation between a high incidence of infrapopliteal surgical reconstructions and a low incidence of amputations was found in a Finnish study (29). Long-term limb salvage rates after infrainguinal bypass surgery in limbs with CLI are presented in Table 3.

Femoral endarterectomy and profundaplasty

Although isolated use of endarterectomy and profundaplasty is relatively rare, they have remained as important adjunct inflow treatments to improve graft patency in infrainguinal bypasses (4). They can also be combined with PTA or stenting during simultaneous endovascular and surgical interventions.

2.3.3. Complications of invasive treatment

In general, the frequency of systemic nonfatal complications has been higher in surgical than in endovascular procedures (8.5 % vs. 1.3 %) (59). High risk cardiac patients with CLI had considerably fewer perioperative cardiac complications when treated by endovascular procedures instead of bypass surgery (135). In claudicants, the risk of limb loss because of failed infrainguinal bypass surgery was 0.24 % (1/409) (133), and 0.18 % (7/3873) because of complications associated with endovascular treatment (28). In patients who had undergone bypass surgery for CLI, graft thrombosis was the most common cause of major amputation (136).

Wound and graft infections especially in synthetic grafts, haemorrhage, thrombosis, lymphoceles, distal embolization, arteriovenous fistulas and anastomotic pseudoaneurysms are procedure-related complications associated with bypass surgery (2, 133). Common complications associated with infrainguinal PTA are puncture site hematomas (2-8 %) or pseudoaneurysms (1 %), distal embolizations or thromboses (1-8 %), arterial wall injury, flow-limiting dissections, perforation, arteriovenous fistulas and contrast-induced renal failure (137, 138). In femoropopliteal PTA, complication frequency has been associated with a higher number of treated segments (66).

Thirty-day mortality rates vary according to the severity of ischemia, patient population and the procedure itself. Thirty-day mortality rates of 2-15 % with a mean of 6.6 % for axillofemoral bypasses have been reported (103, 105-107, 109, 111, 139-141). Operative mortality following PTA for claudication has been 0-0.2 % (28, 52) and 0-2 % in infrainguinal bypasses for claudication (81, 133). For CLI patients, the 30-day mortality rates have been higher: 0-4 % after endovascular treatment (28, 52, 69, 86, 87), and 3-7 % following infrainguinal bypass surgery (24, 40, 83, 134). Operative mortality is most commonly associated with complications of coronary artery disease (69, 83, 109, 142).

2.3.4. Limitations of invasive treatment

When considering invasive treatment for limb ischemia, the anticipated hemodynamic and symptomatic benefit has to be greater than the risk of complications. Patients with CLI are often inoperable or the operative risks are high because of advanced age and comorbidities (30). By the time such patients seek help, ischemia has sometimes progressed beyond the limits where the limb is still salvageable. In some instances, revascularization is not technically possible: long occlusions and diffuse lesions are not amenable to PTA, whereas lack of suitable outflow vessel can make bypass surgery impossible. A shortage of suitable autogenous veins or a likelihood of their later use in coronary surgery have to be considered, because patients with PAOD, even without clinically manifest cardiac disease, have increased risk for cardiac events (143). Although invasive treatments, both endovascular and surgical, have been shown to improve quality of life more than training or no treatment in claudicants, levels of physical dysfunction have remained higher than in healthy controls, possibly because of the underlying generalised atherosclerosis (13).

2.3.5. Survival after invasive treatment

PAOD requiring invasive treatment is associated with considerably decreased life expectancy. Cumulative survival following axillofemoral bypass has been 26-43 % at five years (107, 144). Five-year survival rates after infrainguinal bypass surgery have been 85-86 % in claudicants (81, 133) and 48-66 % in patients with CLI (81, 83, 133). Factors associated with increased mortality after infrainguinal bypass surgery have been ankle pressure lower than 50 mmHg, ABI less than 0.4, diabetes, ongoing CLI (85) and coronary artery disease (81). A 51 % survival rate at five years was reported after PTA for CLI (69).

3. AIMS OF THE PRESENT STUDY

The main purpose of the present study was to define the long-term outcome of limbs with chronic ischemia, claudication or CLI, after endovascular and surgical revascularizations. The specific aims were:

I To analyse long-term primary and secondary patency and limb salvage rates following axillofemoral bypass surgery

II To describe the long-term outcome of infrainguinal bypass surgery in terms of reoperations, primary and secondary patency rates in claudicants, and limb salvage and life with limb rates in critically ischemic limbs

III To define the final outcome of limbs treated with infrainguinal PTA for CLI in terms of reoperations, limb salvage, patient survival and life with limb rates

IV To determine the long-term outcome of limbs with claudication after infrainguinal PTA including primary and secondary patency rates

V To determine the long-term outcome of patients who have undergone invasive infrainguinal, primarily endovascular treatment for claudication in terms of clinical success, total patency rate including crossover between endovascular and surgical revascularization methods, and development of CLI despite invasive treatments

4. PATIENTS AND METHODS

The study population consisted of 585 consecutive patients with 784 treated limbs who had undergone lower limb revascularization in Kuopio University Hospital between 1985 and 1996. Demographic data for the whole patient population are shown in Table 6. Patients treated with femorodistal or axillofemoral bypass surgery or with infrainguinal PTA during the study period were identified by reviewing operating room and angiolaboratory registries. Altogether 273 patients participated in prospective PTA trial during 1989-1992 (145). Most patients were treated for chronic limb ischemia: 22 (3.8 %) operations were for other indications (I, II).

Table 6. Basic characteristics of the study patients.

Parameter	Number
Total patients	585
Male	384 (66)
Female	201 (34)
Total limbs	784
Associated diseases	
Coronary artery disease (ischemia on ECG, history of angina, myocardial infarction, coronary artery bypass grafting)	324 (55)
Hypertension (medication or blood pressure >160/90 mmHg in serial measurements)	298 (51)
Hyperlipidemia (serum cholesterol >6.5 mmol/l or serum triglycerides >2.0 mmol/l)	227 (47)
Diabetes	224 (38)
Cerebrovascular disease (stroke or transient ischemic attack)	120 (21)
Renal insufficiency (serum creatinine >150 µmol/l)	25 (4)
Positive smoking history (current smoker or stopped <10 years ago)	219 (37)

Note.— Numbers in parentheses are percentages. The mean age of the patients was 68 years (range 16-91) years.

Approval of the Kuopio University Hospital ethical committee was obtained (10/89, 100/97, 58/99).

4.1. Preoperative assessment

Patients were first examined by a vascular surgeon either at the outpatient or emergency clinic. AB-indices at rest were measured. The treadmill exercise test (4 minutes, 5 degrees incline, 3.6 km/h) was performed by claudicants to verify the existence of peripheral atherosclerosis and to measure maximal walking distance. DSA of the distal aorta and runoff vessels was routinely performed prior to procedures. Angiograms were analysed by a vascular radiologist to score the limbs by the number of arteries with hemodynamically significant disease (>50 % diameter stenosis). The score was from zero to ten, including common and external iliac arteries, common, deep and superficial femoral arteries, popliteal artery, tibioperoneal trunk, anterior and posterior tibial arteries, and peroneal artery. Distal run-off was assessed by counting the patent calf arteries reaching the ankle.

4.2. Description of procedures and outcome

4.2.1. PTA procedures

Angioplasties were performed in an angiography suite where digital fluoroscopy and road-mapping were available. An ipsilateral femoral antegrade puncture was primarily used. Contralateral femoral access was used for femoropopliteal PTA if occlusive changes at the origin of the SFA made an antegrade approach unsuitable, and popliteal access if the antegrade technique failed, or in the presence of short proximal SFA occlusions. Lesions were visually assessed by the performing interventional radiologist. Balloon diameter was selected to be equal to that of the artery, which was electronically measured with the aid of the DSA software calibrated with a radioopaque external ruler. Lesions were traversed with a special steering catheter (Pier, Cordis Inc., Roden, the Netherlands) with the aid of Glidewire (Terumo, Piscataway, NJ, USA) and dilated with a 5-F balloon angioplasty catheter. When more than one lesion was treated, the sequencing was from proximal to distal. Stenting was performed in two limbs and directional atherectomy in six (IV, V) to make the primary result acceptable. Fibrinolytic therapy was not used before PTA procedures, but in eight cases with complicating thrombosis or embolism 100 000-500 000 units of urokinase was selectively given into the occluded artery (III).

4.2.2. Surgical bypasses

Surgical techniques conformed to standard principles both in axillofemoral and infrainguinal bypasses. In axillofemoral bypasses (I), the axillary artery was used as a donor artery. Distal anastomoses were performed on the common femoral or the deep femoral arteries. Femoral endarterectomy or profundaplasty was performed if necessary. If an axillobifemoral graft was constructed, a side-arm was attached to the axillofemoral graft in the ipsilateral groin near the distal anastomosis, passed through a suprapubic subcutaneous tunnel, and anastomosed to the contralateral femoral artery or its branches.

In infrainguinal bypasses, autologous vein was used if available. Distal anastomosis was made to crural arteries only if more proximal vessels were not usable. If necessary, femoral endarterectomy or profundaplasty was performed to improve inflow.

4.2.3. Complications

Major complications cause death, permanent disability, necessitate invasive treatment or prolong hospital stay, while minor complications require no specific treatment or prolonged hospital observation (2). Systemic complications are either reported separately or included in major complications. Early graft occlusions or PTA failures were not included as complications.

4.2.4. Patient follow-up

Patients had postoperative follow-up visit at 1 month, and further visits were arranged according to the clinical situation. Patients treated with PTA for claudication had follow-up examinations at 1, 3, 6 and 12 months after the primary PTA. Yearly outpatient visits were arranged thereafter up to three years, and further visits were arranged according to the clinical situation (IV). Late follow-up visits were organised during 1996 (I), 1997-1998 (II, V) and 1999 (IV, V).

All follow-up examinations consisted of pulse palpation including the graft in surgical patients, and determination of ABIs using a hand-held Doppler. Infrainguinal grafts were screened by a radiologist with colour doppler ultrasound from the groin down its entire length to below the distal anastomosis including the first centimetres of the recipient run-off artery (II). A decrease in peak velocity to less than 45 cm/s at any point over the graft and its two anastomoses was used as the velocity criterion for graft stenosis (134). Furthermore, transformation of the graft velocity waveform from a triphasic to a monophasic or biphasic configuration coupled with a decrease in peak systolic flow velocity indicated an occlusive lesion (134). Attention was also paid on local acceleration of peak velocity at the area of visualised stenotic lesion. Angiography was performed in cases of subjective and objective deterioration, if further revascularizations were planned.

4.2.5. Outcome parameters

Clinical long-term outcome was assessed as improvement in the Fontaine classification (Table 1) and positive rating on the Rutherford scale (Table 7) (2). Patency rates were based on either maintenance of the achieved improvement in the ABIs (no more than 0.10 below the highest postoperative index), or duplex US or angiography findings indicating a patent segment (2). Primary patency refers to uninterrupted patency at the treated segment or graft with either no procedure performed on it or a procedure to deal with disease progression beyond the treated segment or graft. If patency of the treated segment or graft was maintained or restored with a similar procedure as the primary one (endovascular or surgical), it was listed under secondary patency. "Redo" reconstructions were not included in secondary patencies. Total patency refers to patency maintained at the primarily treated segment(s) by means of any invasive (endovascular and/or surgical) treatments (V). It includes limbs after potential crossover to another treatment group: limbs with primary endovascular treatment (PE) which had undergone further surgical revascularization or primarily surgically revascularized limbs (PS) that required endovascular reoperation. Limbs with primary technical failure or loss of patency within 24 hours of the procedure were included in patency analyses. Beyond the last date of objective proof of patency, limbs were considered lost to follow-up for patency analyses.

Table 7. Rutherford scale for gauging changes in clinical status.

+3	**Markedly improved:** No ischemic symptoms, and any foot lesions completely healed; ABI increased to more than 0.90
+2	**Moderately improved:** No open foot lesions; still symptomatic but only with exercise and improved by at least one category*; ABI not normalised but increased by more than 0.10
+1	**Minimally improved:** Greater than 0.10 increase in ABI but no categorical improvement or vice versa (i.e., upward categorical shift without an increase in ABI of more than 0.10)
0	**No change:** No categorical shift and less than 0.10 change in ABI
-1	**Mildly worse:** No categorical shift but ABI decreased more than 0.10, or downward categorical shift with ABI decrease less than 0.10
-2	**Moderate worse:** One category worse or unexpected minor amputation
-3	**Markedly worse:** More than one category worse or unexpected major amputation

Note.— * Categories refer to clinical classification (Table 1).

Limb salvage and life with limb rates were determined only for patients treated for CLI. Limb salvage was terminated at the time of major amputation, which refers to amputation above the metatarsal line (2). Life with limb refers to patients who are alive without major amputation in the treated limb (30). Survival data are considered complete, since they are based on records of Statistics Finland in addition to patient files.

4.2.6. Reoperations

Vascular reoperations comprised procedures, which aimed to restore impaired circulation, whereas non-vascular reoperations comprised amputations, fasciotomies and soft tissue operations. The number of total operations include primary procedure, repeated endovascular and surgical revascularizations and non-vascular reoperations including amputations. Indications for vascular reoperations were objectively proved early reobstruction, recurrence of subjective symptoms due to reobstruction during the follow-up, development of CLI in claudicant patients, and inadequate improvement of rest pain and tissue defects in patients with CLI.

4.2.7. Long-term medication

Acetylsalicylic acid (ASA) was used as long-term medication in 68.9 % (361/524) of patients who had undergone infrainguinal revascularization; 15.1 % (79/524) of the patients had oral anticoagulants for other medical conditions or recurrent graft thromboses. Dipyridamol was combined with ASA in 9.0 % (47/524) of patients and used alone in 1.0 % (5/524). Oral anticoagulants were combined with ASA or dipyridamol in 2.1 % (11/524) of patients. Altogether 4.0 % (21/524) of the patients had no permanent anticlotting medication due to contraindications.

4.3. Study settings

4.3.1. Study I

This retrospective study comprised all consecutive (n=84) patients on whom axillofemoral bypass operation was performed between 1985 and 1996 (Table 8). During the same period, 195 aortobifemoral operations were performed for chronic limb ischemia in Kuopio University Hospital. The mean age of these patients was 59 years. The decision to use extra-anatomic instead of aortofemoral bypass was related to the high operative risk of the patients, i.e. advanced age and co-morbidity.

Table 8. Patient characteristics and operative indications for axillofemoral bypass operations in 1985-1996 (I).

Number of patients	84
Men	71 (85)
Women	13 (15)
Mean age (range) / years	68 (41-89)
Preoperative risk factors	
Cardiac	49 (58)
Smoking	36 (43)
Hypertonia	27 (32)
Chronic pulmonary disease	26 (31)
Cerebrovascular	18 (21)
Diabetes	13 (15)
Hyperlipidemia	7 (8)
Renal insufficiency	1 (1)
Indications	
CLI	44 (52)
Rest pain	27 (32)
Ulcer or gangrene	17 (20)
Claudication	28 (33)
Acute vascular incidents	12 (14)
Thrombosis	7 (8)
Embolia	1 (1)
Graft infection	1 (1)
Prosthese occlusion	2 (2)
Ruptured external iliac artery aneurysm	1 (1)

Note.— Numbers in parentheses are percentages.

Seventy-five of 84 (89 %) operations were axillobifemoral, and 9 (11 %) axillo-unifemoral. The right axillary artery was used as the donor artery in 63 % of cases. An externally supported PTFE graft was used in 95 % (n=80) of the cases, while dacron prostheses were used in the remainder. Additional procedures included femoropopliteal bypass employing vein in one patient and PTA to the superficial femoral artery in two patients.

4.3.2. Study II

All 226 patients who underwent femoropopliteal or femorodistal bypass in 1988-1996 were included in this study. The mean age of the patients was 66 years (range 16-91 years). The number of operated limbs was 263; 37 patients had surgery in both limbs. CLI was operative indication in 63.9 % (n=168), and claudication in 32.3 % (n=85) of the bypasses. The presenting symptom was rest pain in 49.4 % (83/168) of the limbs with CLI, ischemic ulcer in 33.3 % (56/168), and gangrene in 17.3 % (29/168). There were also five operations (1.9 %) for acute ischemia, three (1.1 %) for femoropopliteal artery aneurysms, one for post thromboembolectomy haemorrhage (0.4 %) and one for traumatic rupture of the SFA (0.4 %). Venous bypasses constituted 87.5 % of all procedures (230/263), and an in situ –technique was used in 83.9 % (193/230) of vein bypasses. PTFE grafts were used in 76 % (25/33) of prosthetic grafts. Dacron and combi-grafts were used in the remaining eight bypasses. In limbs with claudication, distal anastomosis was made to the proximal popliteal artery in 18 % of the limbs, to the distal popliteal artery in 76 % and to the crural vessels in 6 %. In limbs with CLI, distal anastomosis was made to the proximal popliteal artery in 9.5 % of the limbs, to the distal popliteal artery in 54.2 %, to the crural vessels in 32.7 %, and to pedal arteries in 3.6 %. Femoral endarterectomy or profundaplasty was performed as an additional procedure in 62 limbs (23.6 %). Follow-up was completed in 1998.

4.3.3. Study III

Altogether 100 consecutive CLI patients who were treated by infrainguinal PTA between 1989 and 1992 participated in this prospective study; the number of treated limbs was 116. Characteristics of study patients are presented in Table 9. The strategy was to offer endovascular treatment instead of surgery to all patients with CLI, whenever at least one hemodynamically significant obstructive lesion was accessible to PTA. In general, lesions >20 cm with heavy calcifications were considered inaccessible and those limbs were referred to surgery, unless contraindicated. Limbs which had undergone previous endovascular procedures or vascular surgery were excluded. Indication for treatment was rest pain in 23 limbs (20 %), ischemic ulcer in 50 (43 %), and gangrene in 43 (37 %). Of all PTAs performed, 64.1 % (132/206) were femoropopliteal and 35.9 % (74/206) infrapopliteal. The main lesion was a stenosis in 65 % of the limbs and occlusion in 35 %. There were one to four separate treated lesions per limb (mean 1.8) and the mean total length of the treated segments per limb was 9.0 cm (range 0.5-27.0 cm). The mean length of occlusions was 5.5 cm (range 1-19 cm).

Table 9. Characteristics of patients with chronic limb ischemia who had undergone infrainguinal PTA or bypass surgery.

	Claudication		CLI	
	PTA (IV)	**Surgery (II)**	**PTA (III)**	**Surgery (II)**
Number of limbs	218	85	116	168
Number of patients	173	78	100	147
Sex: male (%)/ female (%)	128 (74) / 45 (26)	64 (82) / 14 (18)	40 (40) / 60 (60)	84 (57) / 63 (43)
Mean age in years (range)	65 (41-90)	64 (28-81)	72 (38-90)	68 (39-91)
Diabetes	43 (25)	11 (14)	76 (76)	77 (52)
Coronary artery disease	99 (57)	35 (45)	47 (47)	76 (52)
Hypertension	90 (52)	39 (50)	59 (59)	72 (49)
Cerebrovascular	34 (20)	18 (23)	28 (28)	30 (20)
Renal insufficiency	3 (2)	2 (3)	10 (10)	16 (11)
Smoking	83 (48)	29 (37)	7 (7)	36 (25)
Patent runoff vessels: mean, median, range	2.1, 3, 1-3	2.3, 3, 0-3	0.4, 0, 0-3	1.1, 1, 0-3
Number of diseased vessels: mean, median, range	3.1, 3, 1-7	2.6, 2, 1-7	5.1, 5, 1-8	4.1, 4, 1-9

Note.— Numbers in parentheses are percentages. Ten limbs from study III and 20 limbs from study IV were included in study II.

Surgical revascularizations during follow-up were performed if improvement of CLI was inadequate, if repeated endovascular treatment was thought to be unsuccessful or unfeasible, if there were no contraindications for surgery, and if surgery was technically possible. There were no patients lost to follow-up: at the end of the follow-up all patients had met the major endpoints of the study (major amputation or death). Surgical revascularization and major amputation were regarded as endpoints of follow-up in analyses which were made to define limb salvage and life with limb rates following PTA, whereas surgical revascularizations were included in the analyses of total limb salvage and major amputation was the only endpoint. Analyses determining factors associated with limb salvage were based on endovascular treatment only. Follow-up was completed at the end of 1999.

4.3.4. Study IV

The population of this prospective study consisted of 173 consecutive patients who were treated with PTA for lifestyle-limiting claudication (absolute walking distance less than 200 metres or manifest deficiency in occupational or recreational activities) between September 1989 and December 1992 (Table 9). Limbs which had undergone previous endovascular procedures or vascular surgery were excluded.

Altogether 313 PTAs on 218 limbs consisting of one to five separate procedures per limb (mean 1.4, median 1) were performed. The main lesion responsible for clinical symptoms was in femoropopliteal segments in all patients. The procedures were solely femoropopliteal in 82.6 % of patients (n=180), femoro- and infrapopliteal in 5.0 % (n=11), and femoropopliteal and iliac in 12.4 % (n=27). The main lesion was stenosis in 45.0 % (n=98) of the limbs and occlusion in 55.0 % (n=120). The average total length of treated lesions per limb was 8.8 cm (range 1-31 cm), the average length of individual lesions was 5.2 cm (range 1-20 cm), and the length of single occlusions was up to 15 cm. The main endpoint of the study was primary patency at the end of 1999.

4.3.5. Study V

The study population consisted of 233 consecutive patients with 304 treated limbs who received infrainguinal endovascular and/or surgical treatments for lifestyle-limiting claudication. Priority in primary treatment was given to endovascular treatments when applicable. Primary procedures were performed between 1989 and 1992. Limbs which had undergone previous infrainguinal revascularization procedures and those with CLI or with main lesions in iliac vessels were excluded.

The mean age of the patients was 66 years (range 43-90 years). The mean absolute preoperative walking distance was 150 m (± standard deviation (SD) 79 m) and the mean ABI 0.65 (± SD 0.19). In all, 79.0 % of the patients had hyperlipidemia, 57.9 % had coronary artery disease, 56.2 % were hypertensive, 33.9 % had diabetes, 17.6 % had cerebrovascular disease and 1.7 % renal insufficiency. Altogether 54.9 % of the patients were current smokers or had stopped smoking less than 10 years earlier.

Procedures were performed for accepted clinical indications. PTA was used if the lesions were judged at a joint meeting of interventional radiologists and vascular surgeons to be technically feasible to endovascular treatment. Generally, these lesions were without heavy calcification, stenoses were shorter than 20 cm, and occlusions were less than 15 cm long. Proximal lesions suitable for endarterectomy or profundaplasty were treated surgically. Relative contraindications for surgery and the absence of good quality saphenous vein favoured the use of PTA.

Primary endovascular treatment was used in 272 limbs (89.5 %) whereas 32 (10.5 %) limbs received primary surgical treatment. There were no statistically significant differences in the preoperative risk factors between the PE and PS groups. However, the length of the treated lesions was statistically significantly longer in the PS group (Table 10). Among the 24 primary vein bypasses, there were 3 above-knee (13 %), 19 below-knee (79 %) and 2 crural (8 %) anastomoses. Endarterectomy or profundaplasty was performed on 8 limbs.

Table 10. Diseased vessels and preoperative runoff in primary endovascular (PE) and primary surgical (PS) groups of invasively treated claudicant patients (V).

Parameter	Total study population (n=304)	PE (n=272)	PS (n=32)	P-value (PE vs. PS)
Number of diseased vessels (mean, range)	2.6, 1-6	2.6, 1-6	2.6, 1-6	n.s.
Total length (cm) of treated lesions (mean, range)	8.7, 1-30	7.9, 1-30	15.8, 2-30	<0.0005
Number of limbs according to the total length of treated lesions				
≤10 cm	224 (74)	210 (77)	14 (44)	
10-20 cm	52 (17)	46 (17)	6 (19)	
>20 cm	28 (9)	16 (6)	12 (38)	
Preoperative runoff (mean, range)	2.0, 0-3	1.9, 0-3	2.2, 1-3	n.s.
Main treated segment				n.s.
Common femoral artery	8	5	3	
Superficial femoral artery	257	230	27	
Deep femoral artery	3	2	1	
Popliteal artery	23	22	1	
Tibioperoneal trunk	5	5	0	
Anterior tibial artery	5	5	0	
Posterior tibial artery	2	2	0	
Peroneal artery	1	1	0	

Note.— Numbers in parentheses are percentages. Runoff was assessed as the number of patent crural vessels reaching the ankle (<50 % diameter stenosis).

Information concerning reoperations, hospitalisations, complications, treatment outcome, development of CLI and amputations is considered complete, since relevant patient data from other hospitals were also reviewed at the end of the study. In this study, thirty-day mortality refers to death within 30 days of any invasive diagnostic or therapeutic procedure (primary or repeated) for lower limb ischemia.

4.4. Statistical analyses

The Pearson chi-square test for discrete variables, the Mann-Whitney U test for ordinal variables and the T-test for continuous variables were used when appropriate. Differences between groups were tested by test proportions. The sign test was used to analyse the significance of change in the values of the same variable. Multiple logistic regression analysis was used to analyse predictors of dichotomous response variables. Cumulative patencies, development of CLI despite invasive treatments, limb salvage, life with limb, and patient survival rates versus time of follow-up were determined by life tables and expressed as cumulative percentages (± standard error of estimate (SEE)). Statistical differences between survival curves were determined by means of the Mantel-Cox and Wilcoxon tests. Variables that reached statistical significance ($p \leq 0.05$) were used as covariates in a stepwise Cox proportional hazards model. Odds ratios (OR) and 95 % confidence intervals (CI) were calculated for statistically significant determinants in multivariate analyses. The Riski-program was used to compare survival rates of patients with those of their age- and sex-matched control population living in the same area. Statistical analyses were performed with BMDP (University of California, Berkeley, CA, USA) and SPSS for Windows (SPSS Inc., Chicago, USA) statistical software.

5. RESULTS

5.1. Outcome of axillofemoral bypasses (I)

5.1.1. Operative complications

The number of major complications was 16 (19 %), including 12 systemic complications. The most common major complications were cardiac complications (n=6). The thirty-day mortality rate was 6 % (n=5), and all these patients were operated on for CLI. The causes of early deaths were cardiac in four patients and stroke in one patient.

5.1.2. Reoperations

Reoperation for limb ischemia was required in 28 patients (33 %) during the follow-up (mean 22 months, range 0-82 months): 24 patients (29 %) underwent vascular and 19 patients (23 %) nonvascular reoperations. Axillofemoral grafts occluded in 18 patients (21 %) during the follow-up. Thrombectomy was used on 27 separate occasions to restore flow into the graft: 44 % (4/9) of the patients with axillounifemoral grafts required thrombectomy, compared with 12 % (9/75) of those with axillobifemoral grafts (p=0.03). One prosthesis had to be removed due to graft infection 56 months after the initial operation.

5.1.3. Patency rates

The primary patency rate in the entire study population was 64 % at three and 57 % at five years, and corresponding secondary patency rates were 67 % and 58 % (SEE <0.10 at all time points). Primary patency rates for claudicants and patients with CLI were 73 % (±0.09) and 88 % (±0.06) at one year, 65 % (±0.11) and 69 % (±0.11) at three years, and 65 % (±0.11) and 57 % (±0.14) at five years. Secondary patencies were 87 % (±0.07) and 94 % (±0.04) at one year, 68 % (±0.13) and 70 % (±0.11) at three years and 68 % (±0.13) and 51 % (±0.14) at five years. Operative indication (claudication vs. CLI) was not associated with either primary or secondary patency rates ($p=0.49$ and $p=0.67$, respectively). Axillobifemoral grafts tended to yield better primary patency rates than axillounifemoral grafts ($p=0.10$).

5.1.4. Amputations and limb salvage

Nine patients (11 %) required major amputation during the follow-up. All amputations were performed on patients primarily operated on for CLI (n=7) or acute vascular incidents (n=2). In patients with chronic limb ischemia, CLI as operative indication was a statistically significant determinant of major amputation ($p=0.03$). In four out of nine patients the graft was documented to be patent at the time of amputation, while in three cases it was occluded and in two patients the status of the graft remained unknown. In patients with CLI, cumulative limb salvage rates were 81 % at one and at three years, and 74 % at five years (SEE <0.10 at all time points).

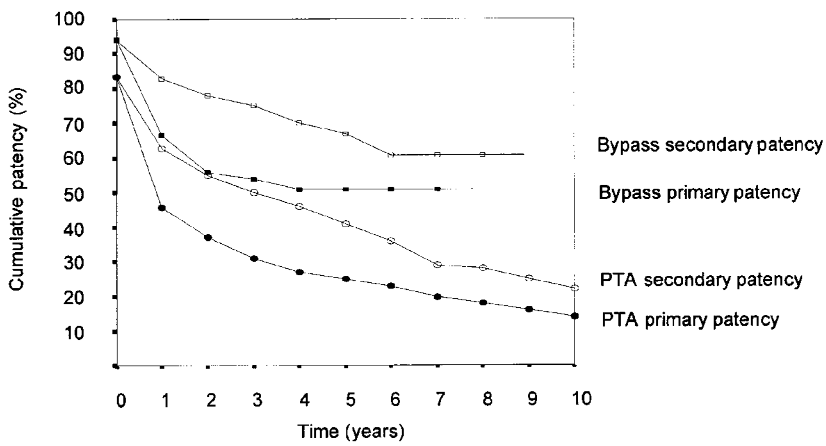
5.1.5. Survival and life with limb rate

Thirty-one patients (37 %) died during follow-up, 18 of them due to atherosclerotic disorders (58 %) and 7 due to malignancies (23 %). Survival rates among claudicants were 82 % (±0.08) at three and 59 % (±0.13) at five years. The corresponding survival rates in patients with CLI were 71 % (±0.07) and 57 % (±0.10) ($p=0.24$). Five years after the primary operation, 50 % of the study patients were still alive, compared with 77 % of the age- and sex-matched control population ($p\leq0.001$). Life with limbs –rates in patients with CLI were 64 % (±0.08) and 40 % (±0.10) at three and at five years.

5.2. Infrainguinal PTA and surgical bypass operations in claudicants (IV, II)

5.2.1. Patency rates

Cumulative primary patency rates in limbs treated for claudication (n=85) were 54 % at three years, and 51 % at five and at seven years after infrainguinal bypass surgery (SEE ≤0.07 at all time points). In limbs treated with PTA (n=218), the figures were 31 % at three, 25 % at five, 20 % at seven, and 14 % at ten years (SEE ≤0.03 throughout the follow-up). Corresponding secondary patency rates after bypass surgery were 75 %, 67 % and 61 %, and 50 %, 41 %, 29 % and 22 % following PTA (SEE ≤0.10 at all time points) (Figure 1).



Limbs at risk	0	1	2	3	4	5	6	7	8	9	10
Bypass primary patency	77	40	26	21	17	8	5	1	-	-	-
Bypass secondary patency	78	54	41	34	25	13	8	4	1	-	-
PTA primary patency	213	88	62	49	42	37	33	27	20	12	2
PTA secondary patency	211	119	93	75	66	58	50	35	24	15	2

Figure 1. Primary and secondary patency rates in patients with claudication according to the primary treatment method (SEE ≤0.10 at all time points) (II, IV).

In the PTA group, a small number of diseased vessels (1-2 vs. 3-7) in the treated limb proved to be the only statistically significant determinant of improved primary patency (p=0.002). Also in surgical bypasses, primary patency tended to be better in limbs with a smaller number of diseased vessels (p=0.08). Short total length of the treated lesions (<10 cm vs. ≥10 cm) was the only predictor of improved secondary patency in limbs with primary PTA (p=0.002), whereas no statistically significant predictors of secondary patency were found in the surgical bypass group.

5.3. Total outcome of infrainguinal revascularizations in claudicant patients (V)

5.3.1. Postoperative period and complications

Of the total 620 invasive therapeutic procedures for lower limb ischemia in patients primarily treated with claudication, 36 (5.8 %) were associated with major complications. Primary treatment led to 12 major complications (12/304, 3.9 %). Seven of these were caused by endovascular treatments (7/272, 2.6 %) and five (5/32, 16 %) by surgical procedures (p=0.004). Treatment of major complications required 21 invasive lower limb procedures during the study, representing 3.4 % of all procedures for limb ischemia. There were no deaths within 30 days after primary procedures, but seven patients (3.0 %) died as a result of complications caused by repeated endovascular (n=2) or surgical (n=5) procedures for limb ischemia. Five of these procedures were performed for CLI and two for claudication.

5.3.2. Reoperations

Figure 2 shows the treatment paths and crossover between the PE and PS groups. No further operations were required during the follow-up on 50.3 % (153/304) of the treated limbs, and no difference was found between the PE and PS groups.

During the follow-up (mean duration 81 months, range 1-146 months), there was a mean of 2.0 (median 1, range 1-10) invasive procedures per limb in the PE group and 2.2 (median 2, range 1-10) in the PS group (p=0.78). Altogether 70.8 % (n=439) of the 620 procedures were endovascular, and 29.2 % (n=181) surgical. Of the 316 repeated procedures, 52.8 % (n=167) were endovascular and 47.2 % (n=149) surgical. The mean number of total hospital days for lower limb ischemia was 15.7 (median 12) in the PS group and 7.7 (median 4) in the PE group (p<0.0005), but there was no difference in the number of hospitalisation periods between the groups (p=0.25).

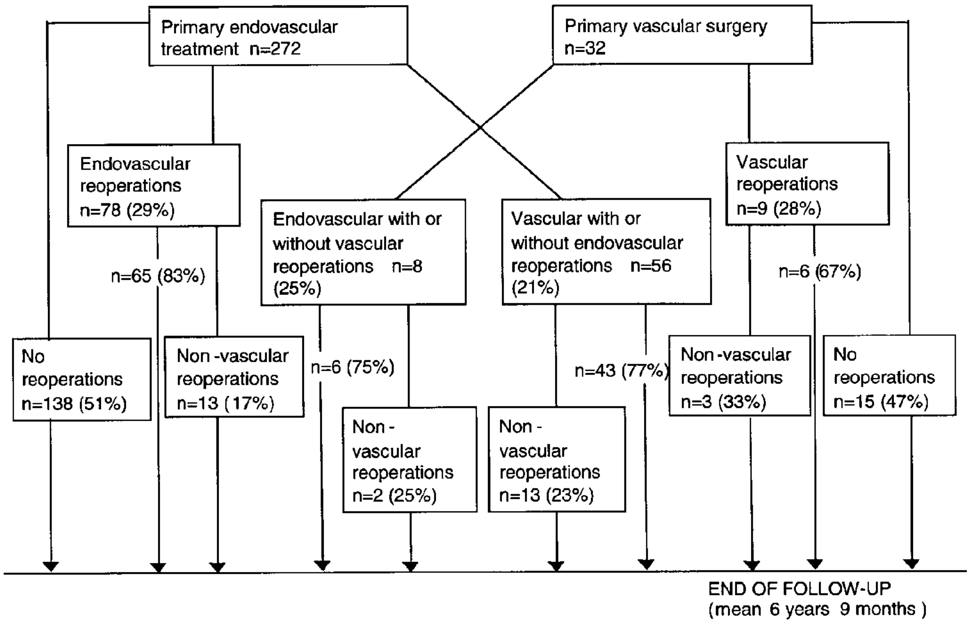


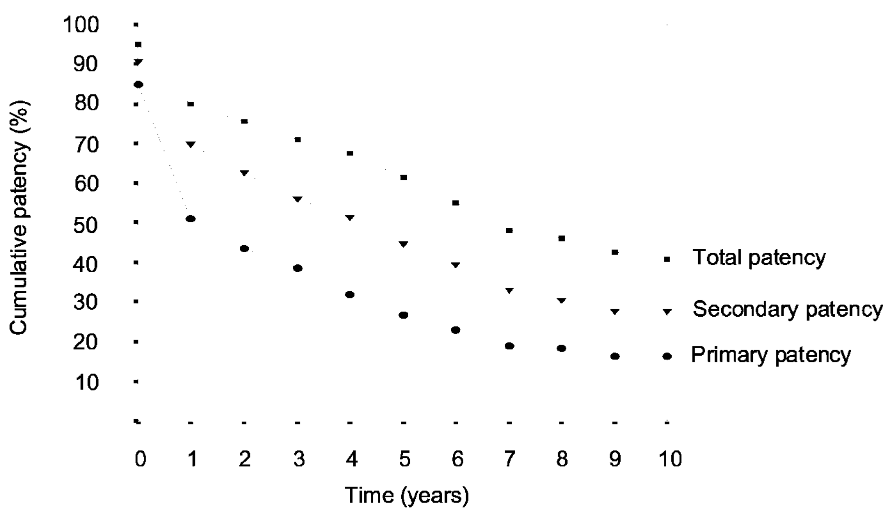
Figure 2. Treatment paths of invasively treated claudicant patients (V).

5.3.3. Long-term clinical outcome

Clinical improvement according to Rutherford's scale (Table 7) was registered in 77.6 % (236/304) of the limbs. Fontaine classifications at the end of the study were statistically significantly better compared with the preoperative values in the total study population and in the PE and PS groups (all p-values ≤0.0005). Outcome in limbs with preoperative Fontaine class 2B (n=208) was better compared with the preoperative state (p<0.0005), whereas those 96 limbs in Fontaine class 2A did not have a statistically significant benefit from invasive treatments (p=0.18). However, in this subgroup also more limbs improved (35 %, 34/96) than deteriorated (23 %, 22/96). The length of the treated lesions or the type of primary treatment were not determinants of late clinical outcome. Furthermore, limbs with treated lesions exceeding 10 cm in length improved statistically significantly in both PE and PS groups and there was no difference between the treatment groups (p=0.78).

5.3.4. Patency rates

Cumulative primary patency rates in the total study population at five and at ten years were 27 % and 16 %, while secondary patency rates were 45 % and 27 %, and total patency rates 61 % and 41 %, respectively (SEE <0.04 at all time points) (Figure 3). Differences between primary, secondary and total patency rates were statistically significant (p<0.01 throughout the study).



Limbs at risk											
Primary patency	287	125	95	75	61	50	40	27	18	8	2
Secondary patency	287	177	141	112	101	85	70	48	31	16	6
Total patency	287	203	172	146	136	118	95	66	42	23	10

Figure 3. Primary, secondary and total patency rates in claudicant patients after infrainguinal revascularization (SEE <0.04 throughout the follow-up) (V).

Among all tested variables, only the type of primary operation (PS instead of PE) proved to be a statistically significant determinant of improved primary patency ($p=0.003$). The only statistically significant determinant of total patency was reoperations. Limbs having undergone vascular reoperations had better total patency rates compared with limbs with only one procedure ($p<0.00005$). There was no statistically significant difference in total patency rates between the PE and PS groups ($p=0.14$).

5.3.5. Development of CLI and amputations

Altogether 12.2 % of the limbs (37/304) developed CLI. Hence, the incidence of CLI development was 1.8 % per year. The time period from the primary operation until the development of CLI was on average 61 months (range 2-132 months). Diabetes ($p=0.0004$, OR 3.8, CI 1.8; 7.9) and hypertension ($p=0.01$, OR 3.0, CI 1.3; 7.2) were independent predictors of increased risk of CLI development in multiple logistic regression analysis.

Altogether 4.6 % of the limbs (14/304) required major amputation. Hence, 38 % of limbs which developed CLI were finally lost (14/37). In invasively treated claudicants, poor preoperative runoff with 0-1 patent vessels proved to be an independent risk factor for future major amputation ($p=0.01$, OR 4.6, CI 1.4; 15.3). The type of primary treatment or the length of the treated lesions were not associated with the risk of CLI development or limb loss.

5.3.6. Survival

A total of 111 patients (47.6 %) died. Cardiovascular (n=71, 64.0 %) and cerebrovascular diseases (n=12, 10.8 %) were the most common causes of death. The cumulative survival rate in the total study population was 82 % (±0.02), 54 % (±0.03) and 43 % (±0.05) at five, ten and twelve years, respectively. In the age- and sex-matched control population the five- and ten-year survival rates were 83 % and 60 % (n.s.). The results of Cox analysis showed that patients with diabetes (p=0.0004, OR 2.0, CI 1.4; 2.9), cerebrovascular disease (p=0.01, OR 1.8, CI 1.1; 2.8), renal insufficiency (p=0.02, OR 4.0, CI 1.2; 12.9) and poor runoff with 0-1 patent crural vessels (p=0.04, OR 1.5, CI 1.0; 2.2) had decreased survival after stratification by age.

5.4. Infrainguinal PTA and surgical bypasses in the treatment of CLI (III, II)

5.4.1. Complications

The rate of major complications was 15.5 % (26/168) in limbs with primary bypass surgery (II) and 12.1 % (14/116) in limbs with PTA (III). The thirty-day mortality rate was 2.7 % (4/147) after bypass surgery and 1.0 % (1/100) following PTA.

5.4.2. Reoperations and amputations

The mean duration of the follow-up was 18 months (range 0-110) in limbs with bypass surgery (II). The total number of operations per limb was on average 1.7 (median 1, range 1-6). Altogether 41.1 % (69/168) of limbs with surgical bypass required reoperations during follow-up: 16.1 % of the limbs (27/168) underwent vascular and 34.5 % (58/168) non-vascular reoperations. Major amputation was performed on 33 limbs (19.6 %). According to logistic regression analysis, diabetes (p=0.03, OR 2.5, CI 1.1; 5.9) and distal bypasses (p=0.05, OR 2.2, CI 1.0; 4.9) were independent determinants of limb loss after bypass surgery for CLI.

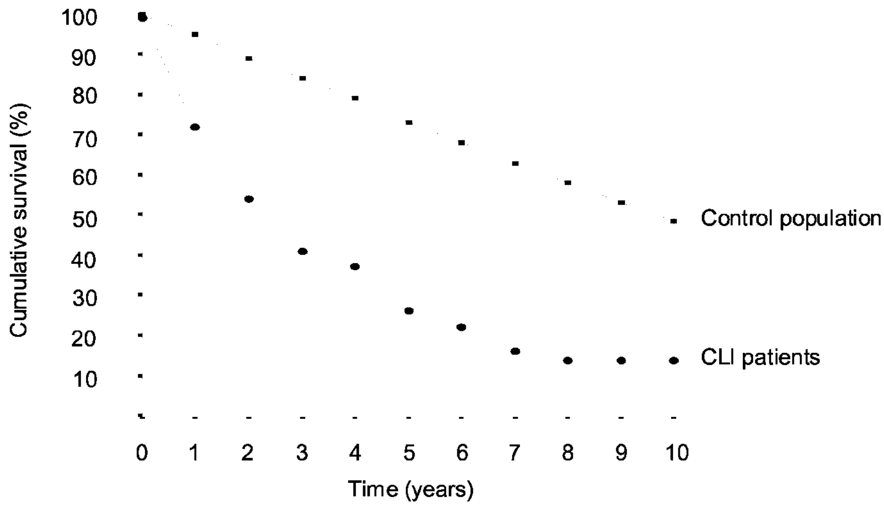
In CLI limbs with primary PTA treatment (III), the mean follow-up period was 38 months (range 0-119) until major amputation or patient death. The average total number of invasive procedures per treated limb was 1.9 (median 2, range 1-6). Reoperations were required on 64 limbs (55.2 %): 27 limbs (23.3 %) required vascular and 51 limbs (44.0 %) non-vascular reoperations. Including limbs which had undergone further surgical revascularizations, the rate of major amputations was 31.9 % (37/116). Diabetics had 2.9 times the risk of major amputation compared with non-diabetics after PTA (p=0.01). There was also a trend towards increased frequency of major amputations among limbs treated for more severe ischemia (rest pain vs. ulcer vs. gangrene, p=0.07).

5.4.3. Limb salvage

Cumulative limb salvage rates after bypass surgery for CLI were 77 % at three, 77 % at five and 60 % at eight years (SEE <0.10 at all time points) (II). The corresponding rates for PTA treatment were 65 %, 60 % and 60 % (SEE ≤0.06 at all time points) (III). In limbs with infrainguinal bypasses, diabetes (p=0.03, OR 2.6, CI 1.1; 6.0) and distal outflow to crural or pedal vessels (p=0.05, OR 2.2, CI 1.0; 4.5) were independent determinants of decreased limb salvage in Cox analysis (II). After primary PTA treatment, a higher number of diseased vessels in the treated limb (6-8 vs. 1-5) proved to be an independent predictor of decreased limb salvage (p=0.004, OR 2.8, CI 1.4, 5.6).

5.4.4. Survival and life with limb rates

The mean age of the patients at the time of the primary intervention was 68 years in surgical patients and 72 years for PTA (Table 9). Cumulative survival was 35 % at five and 21 % at eight years in patients with primary bypass surgery for CLI, and 26 % and 14 % in patients with primary PTA at the same time points (SEE ≤ 0.06 at all time points). In patients who had undergone primary bypass surgery for CLI, renal insufficiency (p=0.0005, OR 4.4, CI 2.0; 9.4), the presence of tissue defect (p=0.02, OR 2.0, CI 1.1; 3.6) and poor runoff with no patent calf vessels (p=0.02, OR 2.0, CI 1.1; 3.4) in addition to advanced age were found to be independent predictors of decreased survival, whereas in patients with primary PTA, coronary artery disease (p=0.001, OR 2.0, CI 1.3; 3.1) and poor runoff (p=0.02, OR 2.7, CI 5.6; 42.3) were found to be predictors of poor survival in the Cox model also after stratification by age. Comparison of survival rates between patients who had undergone primary PTA for CLI and their age- and sex-matched control population reveals a remarkable difference in favour of the control population (Figure 4). Life with limb rates for primary surgical bypasses and PTAs were 35 % and 18 % at five years, and 18 % and 0 % at ten years, respectively (SEE ≤ 0.05 at all time points). Altogether 58 % of the limbs which had undergone PTA for CLI were salvaged until the death of the patient (III).



Patients at risk											
Study patients	100	72	54	41	37	26	22	14	9	5	-

Figure 4. Cumulative survival of study patients with CLI who had undergone primary PTA compared with that of the age- and sex-matched control population (SEE ≤0.05 throughout the follow-up) (III).

6. DISCUSSION

The study population of 585 consecutive patients and 784 treated limbs with follow-up periods up to 12 years made it possible to determine the long-term outcome of axillofemoral and infrainguinal bypasses and infrainguinal PTAs in the treatment of lower extremity ischemia. Patient material of the present study can be considered representative of patients with limb ischemia in medium-sized and large hospitals. Outcome of invasive treatment in claudicant and CLI patients was reported separately. Between these two populations of patients, there are differences in age, the distribution and severity of atherosclerotic lesions, the risk factors affecting treatment decisions, treatment objectives and outcomes, and patient survival. In the literature, long-term outcomes of these two groups of patients have seldom been reported separately.

Patients treated primarily by PTA were studied prospectively. Although the basis for analysis in primarily surgically treated patients was retrospective, they underwent late follow-up examinations as a part of the study protocol. Outcomes were analysed according to current reporting standards (2). The lack of a conservatively treated control-group is a limitation of this study. However, inclusion of an untreated control group in the study protocols with long follow-up periods in patients with CLI and lifestyle-limiting claudication, where conservative measures have been proven insufficient, would have been ethically questionable and practically impossible. Therefore, comparisons of outcomes between invasive and conservative treatments had to be done with historical controls reported in the literature.

Because of the study design, direct comparisons of outcomes between endovascular and surgical revascularizations are not possible. Solid comparisons of treatment outcomes of two or more methods would require prospective randomised controlled trial. However, presenting long-term outcomes of these two methods side by side should underline the strengths and weaknesses associated with each method when using the described patient selection criteria. Furthermore, randomising patients with peripheral vascular disease to endovascular and surgical treatments is difficult and excludes the majority of patients due to lesion type unsuitable for either therapy (70) or due contraindications for surgery.

Since completion of the primary procedures approximately a decade ago, there have been improvements in for instance imaging techniques such as digital road mapping, in endovascular equipment including small vessel angioplasty balloons with better profile and pushability, and in medication such as antiplatelet therapy with ticlopidin and clopidogrel. In surgery, femorodistal bypasses have become more common. Also, the learning curve in both endovascular and surgical procedures has to be considered. Therefore, it is possible that with current equipment and competence outcome might have been better than what was obtained in the present study.

6.1. Axillofemoral bypass surgery

Axillofemoral bypass can be used in surgical treatment of aortoiliac atherosclerosis in elderly patients with systemic morbidities, producing acceptable long-term outcome and moderate operative risk. Patients treated with axillofemoral bypass were older than those who had undergone aortobifemoral bypass in study hospital during the same time period. Furthermore, in many patients with axillofemoral bypass the operative risk factors were high: for instance, 58 % had coronary artery disease compared with 48 % in patients with infrainguinal bypass surgery (II). Long-term patency and reoperation rates of axillofemoral bypasses were comparable with those reported elsewhere (103, 105, 109). Statistically significant improvement in patency rates has been observed in axillobifemoral grafts compared with axillounifemoral grafts in some studies (110, 139, 140). According to other authors, creation of a femorofemoral component might only be efficacious in those patients presenting with bilateral symptoms, since it does not enhance patency rates (105, 107, 109, 144). In the present study, occlusion rate was statistically significantly higher among unilateral bypasses, which tended to yield lower primary patency rates. The achieved limb salvage rate of 74 % at five years in patients with CLI is in line with previously reported results (107, 111). Operative mortality of 6 % encountered in the present study is the average reported for this technique, reflecting the widely spread atherosclerosis and associated comorbidities that the patients undergoing this procedure frequently have.

6.2. Infrainguinal revascularization for claudication

Long-term outcome of infrainguinal bypass surgery in a population of patients comprising only claudicants has seldom been reported (Table 5). In a retrospective analysis, outcome varied according to the level of distal anastomosis and graft material with five year primary patency rates of 48-70 % for femoropopliteal bypasses (133). In a prospective study with 69 % (35/51) claudicants, a 57 % primary patency rate at four years was reported (71). Therefore, the five and seven year primary patency rate of 51 % in infrainguinal bypasses in claudicants in the present study (II) is in accordance with previously reported results.

This is the first study to report ten-year patency rates in claudicant patients after femoropopliteal PTA (IV). Furthermore, in previous studies reporting patency rates at five years, patients with CLI have been included as well (Table 2). Cumulative primary patency of 14 % and secondary patency of 22 % at ten years are modest rates. It has to be noted, however, that among patients treated with PTA in the present study, the length of the treated lesions was longer and the proportion of recanalizations higher than in other series with follow-up periods of three to six years (Table 2). Both increased lesion length and occlusion as lesion type have been reported to contribute to poorer primary patency (52, 66, 72). The number of diseased vessels in the treated limb proved to be the only statistically significant determinant of primary patency in the present study. It can be regarded as a marker of advancement and aggressiveness of the underlying atherosclerotic process.

We evaluated long-term outcomes of non-randomised consecutive claudicant patients who had undergone either primary infrainguinal surgery or PTA. In our treatment strategy the emphasis was on primary endovascular treatment, which is in accordance with the current consensus (5). Generally, stenoses shorter than 20 cm and occlusions less than 15 cm in length without heavy calcifications were treated by PTA. Therefore, many of the endovascularily treated lesions were longer than the current recommendations suggest, although more recently it has been suggested that the range of lesions treated by PTA could be extended to include limbs with more extensive femoropopliteal disease (52). In the present study, the mean length of the treated segments was longer in limbs with primary surgical treatment. On the other hand, there were no statistically significant differences in patient demographics, severity of the atherosclerotic disease, risk factors, runoff or anatomical level of the treatment between the groups. It is notable that in the PS group all the main lesions were in the femoropopliteal segment, whereas the PE group included 13 limbs (5 %) with main lesions in infrapopliteal vessels.

Similar long-term total patency rates up to ten years were achieved in the PE and PS groups, with no differences in reoperation frequencies or degree of clinical improvement at the end of the follow-up. However, endovascular treatment resulted in a statistically significantly lower major complication rate (3 % vs. 16 %) and a smaller number of total hospital days for limb ischemia (8 vs. 16) with an equal number of hospitalisation periods. Furthermore, there were no differences between the groups in the development of CLI or major amputations. On the other hand, primary surgical treatment of claudication resulted in better primary patency rates.

Patients with infrainguinal revascularizations for claudication may require endovascular or surgical reoperations over time due to restenosis, occlusion of the bypass graft or disease progression at a new arterial site. In this study, as many as half of all treated limbs required further invasive treatment during a mean follow-up of 6 years and 9 months. On average, there were 2.0 invasive procedures per limb for lower extremity ischemia, including the primary operation. In a previous study on infrainguinal bypass grafts with a maximum follow-up period of six years, the average number of procedures was 1.8 per limb, and 30 % of primary grafts, excluding early reoperations, required reinterventions (114). In our patients, considerable crossover (21 % of the limbs) between endovascular and surgical treatments was registered, with similar proportions in the PE and the PS groups. Previously, crossover has been reported in 16 % of limbs during a mean follow-up of 19 months (146).

In the present study, the clinical state of the limbs assessed with Fontaine classification was better at the end of the follow-up than before the primary intervention, regardless of the type of primary treatment. According to the Rutherford classification, 78 % of the limbs had continued clinical improvement at the end of the study. Consequently, the beneficial clinical effect of invasive treatments can be considered durable. Patients with severe claudication (preoperative Fontaine class 2B) had a statistically significant clinical benefit from invasive treatment, whereas in milder claudication the difference was not that evident. Statistically significant clinical benefit was observed in limbs with lesions exceeding 10 cm in length irrespective of the primary treatment type. This result implies that endovascular treatment may be indicated in femoropopliteal lesions which are longer than currently recommended.

The concept of total patency is novel (V). All invasive procedures for maintaining total patency and to restore infrainguinal circulation have been included in this analysis. The most important goal clinically is to minimise the symptoms of claudication and to prevent the development of CLI by keeping the diseased infrainguinal segments patent and to treat the potential new lesions of clinical significance with the most appropriate therapy. The analysis revealed that total patency rates were 2.6 times higher than primary, and 1.5 times higher than secondary patency rates at ten years, indicating the value of utilising both surgical and endovascular techniques in the treatment of recurrent ischemia following previous infrainguinal revascularization for claudication.

Some patients with claudication develop CLI in the long-term in spite of invasive treatments. In our subjects, the figure was 1.8 % per year with 12.2 % of limbs developing CLI during the follow-up. In previous studies, the frequency of CLI development has been 2.5-5.1 % per year in untreated claudicants (15, 17). Hence, it seems that invasive treatment of claudication prevents the development of CLI in the long-term, or at least delays it. Data on the risk rate of CLI development following infrainguinal revascularizations for claudication are difficult to find in the literature. Short follow-up periods in the existing reports, especially in endovascular studies, made it difficult to define the frequency of CLI development in spite of revascularization. In this study, CLI manifested a mean of five years after the primary treatment. It has been found previously that invasive treatment in claudication reduced the deterioration of atherosclerotic lesions more than did conservative treatment (54), which could in part explain the phenomenon. In the present study, diabetics and hypertensive patients were at increased risk of CLI. As many as 38 % of limbs developing CLI were finally lost. Not an unexpected result was that claudicant patients with poor runoff were at increased risk of future major amputation.

Mortality among patients with claudication has been found to be 2 times higher than among controls (15), with an expected 5-year survival rate of 60-70 % (16, 21): in the present study the figure was 82 % among patients with a mean age of 66 years at the beginning of the study. At ten years, the cumulative survival rate of our patients was 54 %. Contrary to previous studies, in this study there was only a slight decrease in survival rates between claudicants and their age- and sex-matched control population living in the same area than the study patients. This small difference in comparison with that reported in earlier studies may reflect the improved overall treatment of atherosclerosis and its complications during the last decades, or the generally worse survival in Eastern-Finland populations (the 10-year survival rates for the general population in this age group in Eastern-Finland and in the United States were 60 % and 72 %, respectively (16)).

6.3. Infrainguinal revascularization for CLI

The degree of ischemia was more advanced in patients treated with PTA (III) than in those with bypass surgery (II). Preoperative tissue defect (ulcer or gangrene) was detected in 80 % of the limbs in the former group and in 51 % in the latter. CLI patients treated with PTA were older, and the frequency of diabetes was higher than in patients who had undergone infrainguinal bypass surgery (Table 9). Furthermore, in the former group, the run-off was poorer and there were more diseased vessels in the treated limb. The level of procedures (femoropopliteal vs. crural) was similar in endovascular and surgical treatments with 36 % of crural procedures in both groups. A higher incidence of patients with a positive smoking history was found among surgical patients. Reliable determination of patency rates based on ABI measurements was impossible (III), since the number of diabetic patients, who often have incompressible arteries, was high. Furthermore, ABI measurements were not feasible in gangrenous or pregangrenous lesions of distal limbs.

Thirty-day mortality rates of 1 % for PTA and 3 % for infrainguinal bypass surgery in CLI compare favourably with those reported in the literature. Respective rates have been 0-4 % (52, 69) for PTA and 3-7 % for bypass surgery (40, 83) in patients with CLI. In limbs with bypass surgery for CLI (II), the follow-up period was shorter than in PTA limbs (III), where patients had complete follow-up until major amputation or death. Consequently, straight comparisons of the outcomes are unfeasible. However, in both groups, a greater proportion of reoperations were non-vascular (amputations etc.)

than vascular. As many as 20 % of limbs were lost after bypass surgery during a mean of 18 months follow-up. Major amputation rate of 14 % after a mean of 12 years follow-up has been reported following infrainguinal bypass surgery for CLI (40).

After a completed follow-up with a mean of 38 months, 32 % of limbs with primary PTA for CLI (III) were lost, including amputations following further surgical revascularizations. Altogether 58 % of the limbs survived until the death of the patient. A 7 % major amputation rate has been reported following femoropopliteal PTA with a mean follow-up of two years (72). Among both patients who had undergone PTA and those who had had bypass surgery for CLI (II, III), diabetes was a statistically significant determinant of major amputation: in diabetics the risk of limb loss was 2.5-2.9 times higher than that of non-diabetics. The risk of major amputation was also increased in limbs with distal bypasses compared with femoropopliteal bypasses.

This is the first study to report limb salvage rates extending beyond five years following infrainguinal PTA for CLI (III). The reported three-year limb salvage rates following femoropopliteal balloon angioplasty for CLI have been 76-91 % (72, 80), and 91 % at five years (72) (Table 3). Limb salvage rates in this study with complete follow-up were 65 % at three years, and 60 % at five and at eight years. Limb salvage rates following bypass surgery were 77 %, 77 % and 60 % at three, five and eight years. These rates are in line with those reported in the literature (40, 79-81, 83-85) (Table 3). In the present study, long-term limb salvage rates following PTA and surgical bypass were comparable. Factors associated with decreased limb salvage were similar to those reported by others: diabetes, distal level of outflow (II), and diffuse atherosclerosis in lower limb arteries (III).

Survival was severely decreased in patients with CLI. Factors that were found to be associated with a shorter survival among patients with CLI who had undergone infrainguinal revascularization were poor runoff (II, III), preoperative tissue defect (II), renal insufficiency (II) and coronary artery disease (III), which can be considered markers of severe, widely-spread atherosclerosis.

7. SUMMARY AND CONCLUSIONS

The main purpose of this study was to evaluate the long-term outcome of endovascular and surgical revascularizations in chronic lower limb ischemia and to define outcome determinants. The study comprised 585 patients, with 784 treated limbs, who had undergone axillofemoral bypass surgery or infrainguinal surgical or endovascular revascularization.

Axillofemoral bypass surgery can be used in the treatment of aortoiliac atherosclerosis in elderly patients with systemic co-morbidities. This operation results in acceptable long-term patency, limb salvage and operative mortality rates, but it was associated with rather high risk of major complications. The risk of graft occlusion was higher in axillounifemoral grafts than in axillobifemoral grafts.

In infrainguinal endovascular and surgical revascularizations for claudication, direct comparisons between the groups were unfeasible due differences in the treated lesions within the therapy groups. A higher number of diseased vessels in the treated limb was associated with decreased long-term patency rates. Surgical treatment produced higher primary patency rates. In surgical treatment, the rate of major complications was six times higher and the number of total hospital days two times higher than those of endovascular treatment, with similar numbers of reoperations, long-term clinical improvement and total patency rates. These results were obtained even though the targets treated with PTA included lesions longer than recently recommended. Combining endovascular and surgical revascularizations, if indicated in the course of time, results in considerable improvement in cumulative total patency in the long-term, compared with primary and secondary patencies which include outcome of only a single treatment method. Invasive treatment of mild claudication failed to show statistically significant clinical benefit in the long-term, whereas patients with severe claudication had definite benefit. Survival of claudicant patients did not differ from that of the general population. Comparing the outcome of study patients with that reported in previous studies on the natural history of claudication suggests that invasive treatment of claudication prevented or at least delayed the development of CLI.

In CLI patients with diabetes, the risk of major amputation was almost three times higher than in non-diabetics, both after endovascular and surgical revascularization in infrainguinal vessels. Long-term limb salvage rates were similar in endovascular and surgical revascularizations. The present study confirms the findings of markedly reduced survival in patients with CLI compared with age- and sex-matched control populations.

The results of this work show that

1. Axillofemoral bypass results in satisfactory 5-year patency and limb salvage rates in the treatment of aortoiliac atherosclerosis in elderly patients with high operative risk. The frequency of graft occlusion was higher in axillounifemoral grafts than in axillobifemoral grafts.
2. Infrainguinal bypass surgery results in acceptable 7-year patency and limb salvage rates in patients with claudication and CLI, respectively. The operative mortality rate was low in spite of numerous major complications.

3. One third of limbs with infrainguinal PTA for CLI require eventual major amputation, and the risk is increased in diabetics. A mean of two invasive procedures for limb ischemia were required after the manifestation of CLI. Survival of these patients is very poor.
4. The ten-year patency rate of infrainguinal PTA is low. Patency rates were better in limbs with a small number of diseased vessels and in those with short total length of treated lesions.
5. Combining endovascular and surgical revascularizations in the treatment of infrainguinal lesions in patients with claudication results in improvement in long-term total outcome.

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9. ORIGINAL PUBLICATIONS